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Keywords: folic acid supplements, periconceptional exposure, prenatal exposure, pediatric cancer, pilot study

Prospective Investigation of Periconceptional Folic Acid Supplements and Pediatric and Adult Cancers in the Chinese Children and Families Cohort: A Pilot Study in a Sample of Rural and Urban Families

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Abbreviations: CDC: Centers for Disease Control and Prevention; CIP = Community Intervention Program; FA = folic acid

ABSTRACT

Objective: To determine the feasibility of long-term prospective follow-up and ascertainment of pediatric cancer in offspring and mothers from a 1993-1995 Community Intervention Program (CIP) public health campaign population

Design: Feasibility pilot study for a prospective cohort study

Setting: Families residing during 2012-2013 in one rural and one urban county from 21 counties in 3 provinces in China included in the CIP campaign

Participants: The feasibility study targeted 560 families, including 280 from the rural and 280 from the urban county included in the large original study; about half of mothers in each group had taken and half had not taken FA supplements.

Intervention: The planned new study is observational, with the cohort identified from a community intervention program of periconceptional folic acid carried out to evaluate the associated reduction in neural tube defects in the offspring.

Primary and secondary outcome measures: Incidence of pediatric leukemia, brain tumors and other pediatric cancers in offspring was the primary outcome. Secondary outcomes would be other incidence and mortality from other chronic diseases in offspring and cancers and other chronic diseases in mothers

Results: Only 3.4% of pilot study families could not be found, 3.9% had moved out of the study area, and 8.8% refused to participate. Interviews were completed by 82% of mothers, 79% of fathers, and 83% of offspring in the 560 families, and almost all mothers and offspring who were interviewed also participated in anthropometric measurements. We found notable urban-rural differences in sociodemographic and lifestyle characteristics of the parents, but fewer differences among the offspring. In eight catchment area hospitals, we identified a broad range of pediatric cancers diagnosed during 1994-2013, although pediatric brain tumors, lymphomas, and rarer cancers were likely under-represented.

Conclusions: Overall the pilot study was successful. Next steps and strategies for overcoming the limitations are described.

ARTICLE SUMMARY

Strengths and limitations of this study

- The proposed main Children and Families Cohort Study would provide the only prospective assessment internationally of the relation of *in utero* exposure to periconceptional folic acid supplements with subsequent risk of cancers and other serious chronic diseases in offspring and mothers.
- The current pilot study has shown positive results for re-identifying, tracing, interviewing, and obtaining anthropometric measurements in the population included in the 1993-1995 Chinese Community Intervention Program.
- The main limitation is the fixed size of the original Community Intervention Program study population which limits statistical power, given the rarity of pediatric leukemia and other pediatric cancers.
- A larger feasibility study over a broader geographic region in the catchment area is needed to verify that the original study population can be reassembled with high participation rates, that close to complete ascertainment of pediatric cancers can be achieved, and that matching pediatric cancers identified in catchment area and associated referral hospitals with the study population is feasible.

INTRODUCTION

Environmental factors and gene-environment interactions during the periconceptional, prenatal, and early-life periods are increasingly linked with cancer and other serious diseases during childhood, adolescence and adulthood, but research is limited and mechanisms are poorly understood.[1, 2] Biological evidence implicates prenatal exposures based on the same chromosomal rearrangements found in Guthrie cards obtained at birth as seen subsequently in children who develop pediatric leukemia.[3] The only established risk factors (*e.g.* ionizing radiation, a few genetic or congenital syndromes, and birth weight)[4] explain less than 20% of occurrence.[5, 6] Modest increased [7-10] or reduced risks [11, 12] have recently been linked with other exposures in pooled pediatric leukemia case-control studies. Prospects for prevention are limited to avoidance of ionizing radiation or high birth weight, although more recently periconceptional folic acid supplements have been linked with reduced risks in a large pooled analysis.[11] However, results for the association of periconceptional or prenatal folic acid supplements and pediatric leukemia have been inconsistent in individual studies, and these inconsistencies and the modest associations observed in the pooled analysis may be due in part to differential or inaccurate long-term recall,[13, 14] selection bias[15] and/or declining participation rates, and growing socioeconomic differences between control and case subjects.[16-18] Prospective large epidemiologic studies could overcome many of these limitations.

A unique opportunity to evaluate the potential role of periconceptional folic acid supplements in reducing risk of pediatric leukemia in offspring was identified 20 years after a 1993-95 Community Intervention Program (CIP) in which periconceptional and first trimester FA supplements were provided in 21 Chinese counties to reduce neural tube defects (NTD). Among offspring of 130,142 women who took 400 mcg supplements compared with offspring of the 117,689 women who did not take FA supplements during the periconception period, there was a 79% and 41% reduction in the prevalence of NTD in high (northeast) and lower (southeast) rate regions, respectively.[19] Extensive information had been collected during 1993-1995 on maternal sociodemographic, lifestyle, reproductive, medical conditions and treatments, and other factors during the periconceptional, prenatal, and early neonatal periods.

We conducted a pilot study to assess the feasibility of: (1) establishing a large cohort (designated the Children and Families Cohort Study (CFCS) from the CIP families for planned prospective epidemiologic studies evaluating pediatric leukemia and other health outcomes in offspring and mothers; (2) collecting data from two generations of family members by interview and anthropometric measurements; and (3) identifying and validating pediatric cancers diagnosed during 1994-2013 in the catchment area among children who are potentially eligible CIP offspring.

METHODS

Study team organization and approvals

In 2012-2013 investigators from the Chinese Center for Disease Control and Prevention (China CDC), U.S. Centers for Disease Control and Prevention (US CDC), the U.S. National Cancer Institute (NCI), the Maternal and Child Health (MCH) Hospital leaders of each county, and clinicians of the hospitals selected for identification of pediatric cancers conducted data collection. The protocol was approved by the provincial, city, and county health bureaus, county

MCH hospitals and other participating hospitals, and by the Chinese and US CDCs and US NCI ethics review committees (see details in Ethics Approval section following the Discussion).

Study sample

Five hundred CIP families were targeted from two CIP geographic regions, *e.g.*, a rural county in the northeast and an urban county in the southeast. From the pregnancy-monitoring registration system, 280 families from each county were selected with eligibility criteria including: 1) mother resided and underwent a premarital or prenatal physical exam in the specified county during 1993-1995; 2) the pregnancy resulted in a live, single birth in the county by December 1996; 3) sex of the infant was known, and 4) high quality data on maternal use of FA supplements before and during the pregnancy was available.

Tracing and contacting families

County MCH staff verified the names, vital status, current addresses, and phone numbers of eligible mothers and children selected by comparing the lists with township and village health service and New Rural Cooperative Insurance rosters. To improve recruitment, the county-level MCH, township Hospital, village or community health service center physicians, assisted by the village development and community/street committee staff, made initial contact with the families.

A letter describing the study purpose, questionnaire topics, and physical measurements, confidentiality, benefits, potential risks, incentives, and opportunity to opt out of all or part of the data collection was mailed or delivered in person. After letter delivery, the village or Township doctor contacted the mother/caretaker to answer questions, and arrange a home visit where consent was obtained.

Interviewer training

After a didactic 2-day training, interviewers practiced questionnaire administration and taking anthropometric measurements. The training concluded with instructions on manual review and data editing. Approximately one month later, supervisory Chinese CDC staff again evaluated staff, and re-trained as needed.

Data collection: questionnaires

One of two questionnaires assessed family residential characteristics and maternal sociodemographic characteristics, lifestyle, reproductive and medical history, and job history. If the child resided with a caretaker, a modified shorter questionnaire was administered. A second maternal/caretaker questionnaire asked about the offspring's date of birth, vital status, history of cancer or birth defects, diagnosis of autism, developmental milestones, highest level of education, and job history.

The offspring's questionnaire asked date of birth, self-rating of physical health, source of medical care, number of non-routine health visits in the past 12 months, cigarette smoking and second-hand smoke history, use of alcohol, and history of pubertal changes.

The father's questionnaire inquired about date of birth, education, marital status, job history, smoking and second-hand smoking, alcohol use, and medical history.

Other data collection (results reported separately)

After the interviews, offspring and mothers were invited to participate in anthropometric measurements at the Township hospitals. At the end of questionnaire and anthropometric measurements data collection, the participants received appreciation certificates and incentives. A letter was also provided indicating that the participant might be contacted for a second study to assess diet, nutrition, physical activity, and ultraviolet radiation exposure.

Identification and validation of pediatric cancer cases

In consultation with hospitals and community leaders, 8 hospitals providing different levels of services were selected from study regions and major cities near to the catchment area where CIP children might have been referred for diagnosis and treatment of pediatric cancer. A workshop was held with experts in pediatric hematology, oncology, and neurosurgery from these hospitals to develop the methods for identification and validation of the pediatric cancer outcomes.

The medical record review process included: (1) searching for medical records to identify all pediatric cancer patients born during 1994-1996 who were diagnosed and/or treated during 1994-2013; (2) developing a list of all potentially eligible patients (born during 1994-1996 in the 21 counties included in the CIP or, if no specific place of birth was listed, those born in the three provinces in which the 21 counties were geographically located); (3) obtaining and abstracting medical records of these patients; and (4) independent reviewing of the abstract forms by two clinical experts with resolution of differences through discussion to determine a final diagnosis. For quality control purposes, each hospital was visited at least once by China CDC staff to evaluate procedures. In the absence of re-identification of the entire CIP cohort and comprehensive population-based cancer registries, it was not possible to link the pediatric cancer cases identified in hospitals with the cohort.

Data management

A data management training workshop was held in Beijing for China CDC staff followed by a detailed data review and cleaning. All forms were coded, checked, entered twice, and data verified for accuracy. Range and logic sequences were verified against original paper forms and corrections made as required.

Statistical analysis

In data analysis conducted during 2016-2017, cross-tabulation was used to evaluate the distribution of demographic, socioeconomic, lifestyle, developmental and medical history characteristics by county. Chi-square tests were used to test for urban versus rural geographic differences by covariates among mothers, offspring, and fathers.

Subject involvement

Subjects were informed about results of anthropometric measures and blood chemistry laboratory tests (methods for these aspects of a second pilot study reported elsewhere). Subjects also received physical activity monitors at the end of the physical activity monitoring component of the second pilot study (methods reported elsewhere).

RESULTS

Of the 560 families selected for the pilot study, only 3% (2% in the rural and 5% in the urban center) could not be found, 4% of families reportedly moved away (6% in the rural and 2% in the urban center), and 9% (8% in the rural and 9% in the urban center) refused to be contacted (Table 1). Overall, 82% of mothers, 79% of fathers and 83% of offspring completed interviews of the 560 families selected. Among the 469 families (84% of the 560 selected) targeted for interviews (after exclusions) the interview participation was very high, e.g., 98% of mothers, 95% of fathers, and 99% of offspring. Almost all mothers and offspring who were interviewed also participated in the anthropometric measurements (Table 1). The proportion of mothers contacted who took FA supplements (49% in the rural center, 52% in the urban center) was similar to the 50% in each center who took FA in the samples originally selected.

Table 1. Population targeted for pilot study, description of participants, reasons for non-participation, and residential and sociodemographic characteristics of participating families

Population targeted, description of participants and reasons for non-participation in pilot study	Rural area N (%)	Urban area N (%)	Both areas N (%)	P-value*
Number of families selected for pilot	280	280	560	
Families selected but not included	46 (16.4%)	45 (16.1%)	91 (16.3%)	
Reason not included				
Moved away	17 (6.1%)	5 (1.8%)	22 (3.9%)	
Not found	6 (2.1%)	13 (4.6%)	19 (3.4%)	
Refused	23 (8.2%)	26 (9.3%)	49 (8.8%)	
Mother deceased	0	1 (0.3%)	1 (0.1%)	
Families targeted for interviews†	234 (83.6%)	235 (83.9%)	469 (83.8%)	
Mothers who consented among families targeted for interview	229 (97.9%)	231 (98.3%)	460 (98.1%)	
Mothers: Completed interview‡	229 (81.8%)	231 (82.5%)	460 (92.1%)	
Physical measurements§	228 (99.6%)	230 (99.6%)	458 (99.6%)	
Fathers: Completed interview‡	232 (82.9%)	212 (75.7%)	444 (79.3%)	
Children: Completed interview‡	233 (83.2%)	229 (81.8%)	462 (82.5%)	
Physical measurements§	231 (99%)	229(100%)	460 (99.6%)	
Caretakers: Completed interview¶	6	9	15	

Residential and sociodemographic characteristics of participating families				
Number of years at current home				
<=10	23 (10%)	111 (48%)	134 (29%)	<.0001
11–19	138 (59%)	76 (33%)	214 (46%)	
20+	71 (31%)	45 (19%)	116 (25%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Own or rent home				
Own	224 (97%)	216 (93%)	440 (95%)	0.0380
Rent	7 (3%)	17 (7%)	24 (5%)	
Unknown	1 (0.4%)	0	1 (0.2%)	
Highest number of persons residing in residence in the past year				
<=3	100 (43%)	97 (42%)	197 (42%)	<.0001
4	83 (36%)	26 (11%)	109 (23%)	
>=5	49 (21%)	110 (47%)	159 (34%)	

*Chi-square test for rural vs urban differences
†Targeted for interviews were those who had not moved away, could be found, did not refuse, or mother not deceased
‡Percents shown are the proportion completing interviews of those selected for the pilot study
§Percents are the proportions who completed physical measurements of those who were interviewed
¶If mother not available, caretaker information was used

Nearly half of urban families resided 10 or fewer years in their current home whereas 90% of rural families had lived more than 10 years in the current home (Table 1). More than 93% of rural and urban families owned their current home. Close to half of the urban families compared to 21% of rural families had 5 or more persons recently residing in their residence.

Urban mothers were younger at the age of marriage registration, birth of the CIP offspring, and at the age of current interview completion (Table 2). Rural mothers reported less education, held fewer jobs, and a slightly higher proportion were married compared with urban mothers. Almost none of the rural and urban mothers reported smoking cigarettes. Rural mothers (43%) were somewhat more likely than urban mothers (33%) to report being exposed to secondhand smoke during their pregnancies for 3 or more days per week. Rural mothers (45%) were more likely than urban (35%) to report that their offspring had been exposed to secondhand smoke 3 or more days per week before age 5 years. Few of the mothers (5% overall, 8% urban versus 1% rural) reported drinking alcohol. Rural mothers were more likely to report onset of menstrual periods at older ages, and 30% of rural compared with 16% of urban mothers reported only one pregnancy.

Table 2. Maternal sociodemographic, lifestyle and reproductive characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=229 (%)	Urban area N=231 (%)	Both areas N=460 (%)	P-value *
Age at CIP enrollment / marriage registration				
<=22	84 (37%)	126 (55%)	210 (46%)	0.0002
23-24	66 (29%)	59 (26%)	125 (27%)	
>=25	79 (34%)	46 (20%)	125 (27%)	
Age at first birth				
<=23	88 (38%)	132 (57%)	220 (48%)	<.0001
24-25	58 (25%)	57 (25%)	115 (25%)	
>=26	83 (36%)	42 (18%)	125 (27%)	
Age at CFCS interview completion				
<=39	70 (31%)	116 (50%)	186 (40%)	<.0001
40-41	72 (31%)	67 (29%)	139 (30%)	
>=42	87 (38%)	48 (21%)	135 (29%)	
Highest level of education				
None	3 (1%)	1 (0.4%)	4 (1%)	<.0001
Some or all elementary school	42 (18%)	17 (7%)	59 (13%)	
Completed middle school	144 (63%)	143 (62%)	287 (62%)	
Completed high school/ technical school	39 (17%)	46 (20%)	85 (18%)	
Completed some or all college/university	1 (0.4%)	24 (10%)	25 (5%)	
Current marital status				
Married	227 (99%)	216 (94%)	443 (96%)	0.0002
Widowed	2 (1%)	1 (0.4%)	3 (1%)	
Divorced	0	12 (5%)	12 (3%)	
Other	0	2 (1%)	2 (0.4%)	
Current number of jobs after completed school				
None	0	1 (0.4%)	1 (0.2%)	<.0001
1	158 (69%)	21 (9%)	179 (39%)	

Characteristics	Rural area N=229 (%)	Urban area N=231 (%)	Both areas N=460 (%)	P-value [*]
2	48 (21%)	68 (29%)	116 (25%)	
3+	23 (10%)	141 (61%)	164 (36%)	
Smoking/Secondhand Smoke [*]				
Never smoked cigarettes regularly	227 (99%)	230 (100%)	457 (99%)	0.6225
Exposed to secondhand smoke at home >10 years before age 20	91 (40%)	79 (34%)	170 (37%)	0.2884
Exposed to secondhand smoke at home >10 years after age 20	125 (55%)	122 (53%)	247 (54%)	0.5293
Exposed to secondhand smoke during CIP pregnancy for 3 or more days per week	99 (43%)	77 (33%)	176 (38%)	0.0788
Child exposure to secondhand smoke before age 5 years				
None	101 (44%)	105 (45%)	206 (45%)	0.0077
<3 days per week	22 (10%)	43 (19%)	65 (14%)	
3+ days per week	103 (45%)	80 (35%)	183 (40%)	
Unknown	3 (1%)	3 (1%)	6 (1%)	
Ever drink alcohol				
No/less than once per month	226 (99%)	213 (92%)	439 (95%)	0.0012
Yes	3 (1%)	18 (8%)	21 (5%)	
Age menstrual periods started				
12-13	29 (13%)	47 (20%)	76 (17%)	0.0480
14-15	120 (52%)	122 (53%)	242 (53%)	
16+	78 (34%)	62 (27%)	140 (30%)	
Unknown	2 (1%)	0	2 (0.4%)	
Number of pregnancies				
1	68 (30%)	37 (16%)	105 (23%)	<.0001
2	95 (41%)	86 (37%)	181 (39%)	
3	53 (23%)	74 (32%)	127 (28%)	
4+	13 (6%)	34 (15%)	47 (10%)	

[*] Chi-square test for rural vs urban differences

Rural fathers were older at the time of marriage registration, birth of their offspring, and at the current interview compared with urban fathers (Table 3). Rural fathers reported less education and fewer jobs compared with urban fathers. A higher proportion of rural (33%) compared with urban (19%) fathers reported never smoking, although rural fathers were more likely than urban fathers to be exposed to secondhand smoke for over ten years before age 20. Urban (75%) compared to rural (60%) fathers were more likely to be currently smoking. Use of alcohol was similar between rural (63%) and urban (65%) fathers, but a somewhat higher proportion of urban (61%) than rural (57%) fathers reported alcohol use for 15 or more years.

Table 3. Paternal sociodemographic and lifestyle characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=232 (%)	Urban area N=212 (%)	Both areas N=444 (%)	P-value *
Age at CIP enrollment / marriage registration				
<=22	77 (33%)	85 (40%)	162 (36%)	0.0031
23-24	56 (24%)	69 (33%)	125 (28%)	
>=25	99 (43%)	58 (27%)	157 (35%)	
Age at birth of child				
<=23	71 (31%)	91 (43%)	162 (36%)	0.0002
24-25	59 (25%)	67 (32%)	126 (28%)	
>=26	102 (44%)	54 (25%)	156 (35%)	
Age at CFCS interview completion				
<=39	58 (25%)	77 (36%)	135 (30%)	0.0039
40-41	68 (29%)	69 (33%)	137 (31%)	
>=42	106 (46%)	66 (31%)	172 (39%)	
Highest level of Education				
None	1 (0.4%)	0	1 (0.2%)	<.0001
Some or all elementary school	43 (19%)	16 (8%)	59 (13%)	
Completed middle school	153 (66%)	125 (59%)	278 (63%)	
Completed high school/technical school	32 (14%)	49 (23%)	81 (18%)	
Completed some or all college/university	3 (1%)	22 (10%)	25 (6%)	
Number of jobs after completed school				
1	146 (63%)	28 (13%)	174 (39%)	<.0001
2	63 (27%)	65 (31%)	128 (29%)	
3+	23 (10%)	119 (56%)	142 (32%)	
Currently smoking cigarettes				
Never Smoked	77 (33%)	40 (19%)	117 (26%)	0.0020
No	16 (7%)	13 (6%)	29 (7%)	
Yes	139 (60%)	159 (75%)	298 (67%)	

Characteristics	Rural area N=232 (%)	Urban area N=212 (%)	Both areas N=444 (%)	P-value *
Secondhand Smoke*				
Exposed to secondhand smoke at home >10 years before age 20	103 (44%)	73 (34%)	176 (40%)	0.0272
Exposed to secondhand smoke at home >10 years after age 20	53 (23%)	56 (26%)	109 (25%)	0.7914
Use of alcohol				
No/less than once per month	86 (37%)	74 (35%)	160 (36%)	0.6353
Yes	146 (63%)	138 (65%)	284 (64%)	
Use of alcohol in years				
Never	86 (37%)	74 (35%)	160 (36%)	<.0001
<15	1 (0.4%)	2 (1%)	3 (1%)	
15-19	8 (3%)	36 (17%)	44 (10%)	
20+	125 (54%)	94 (44%)	219 (49%)	
Unknown	12 (5%)	6 (3%)	18 (4%)	

*Chi-square test for rural vs urban differences

Urban versus rural differences in sociodemographic factors were less apparent among offspring (Table 4). The two groups were similar in birth year, age at interview, and sex distribution, but a somewhat more urban than rural offspring reported living with their parents. Most in each group were full-time students, but urban offspring were more likely to report attending trade or technical school. Most offspring in both groups reported never smoking cigarettes regularly; a somewhat higher proportion of urban than rural offspring reported secondhand smoke exposure at home for 1 or more days per week and alcohol use for one or more days since birth.

Table 4. Offspring sociodemographic and lifestyle characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=233 (%)	Urban area N=229 (%)	Both areas N=462 (%)	P-value*
Year of birth				
1994	67 (29%)	70 (31%)	137 (30%)	0.7636
1995	106 (45%)	96 (42%)	202 (44%)	

Characteristics	Rural area N=233 (%)	Urban area N=229 (%)	Both areas N=462 (%)	P-value*
1996	60 (26%)	62 (27%)	122 (26%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Age at interview completion				
<16	88 (38%)	82 (36%)	170 (37%)	0.5380
16	93 (40%)	102 (45%)	195 (42%)	
17+	52 (22%)	44 (19%)	96 (21%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Sex				
Female	120 (52%)	112 (49%)	232 (50%)	0.5772
Male	113 (48%)	117 (51%)	230 (50%)	
Living arrangements				
Living with parents	211 (91%)	221 (97%)	432 (94%)	0.0001
Living with grandparents or other adult guardian	1 (0.4%)	3 (1%)	4 (1%)	
Other	15 (6%)	0	15 (3%)	
Unknown	6 (2.6%)	5 (2.2%)	11 (2.4%)	
Current activity: school, work, other				
Full-time student	215 (92%)	208 (91%)	423 (92%)	0.2205
Working part-time and attending school part-time	0	3 (1%)	3 (1%)	
Working	6 (3%)	3 (1%)	9 (2%)	
Not working and not attending school	7 (3%)	10 (4%)	17 (3.7%)	
Unknown	5 (2%)	5 (2.4%)	10 (2.2%)	
Highest level of Education				
Junior high school	43 (18%)	18 (8%)	61 (13%)	<.0001
Senior high school	123 (53%)	94 (41%)	217 (47%)	
Trade or technical school	49 (21%)	99 (43%)	148 (32%)	
Unknown	18 (8%)	18 (8%)	36 (8%)	
Ever smoked cigarettes regularly				
No	223 (96%)	215 (94%)	438 (95%)	0.3777
Yes	10 (4%)	14 (6%)	24 (5%)	
Number of days exposed to second hand smoke where you live in past week				
0	158 (68%)	143 (62%)	301 (65%)	0.0275
1-4	33 (14%)	55 (24%)	88 (19%)	
5+	38 (16%)	30 (13%)	68 (15%)	
Unknown	4 (2%)	1 (0.4%)	5 (1%)	

Characteristics	Rural area N=233 (%)	Urban area N=229 (%)	Both areas N=462 (%)	P-value*
Number of days ever drank alcohol since birth				
Never	199 (85%)	133 (58%)	332 (72%)	<.0001
1-2	14 (6%)	40 (17%)	54 (12%)	
3-9	11 (5%)	29 (13%)	40 (9%)	
10-19	2 (1%)	10 (4%)	12 (3%)	
≥ 20	5 (2%)	13 (6%)	18 (4%)	
Unknown	2 (1%)	4 (2%)	6 (1%)	

*Chi-square test for rural vs urban differences

Eight hospitals selected included county and provincial hospitals, children's medical centers, and referral hospitals in the nearby cities of Beijing (treating brain tumors), Tianjin (hematologic disorders), and Shanghai (pediatric oncology) to which children would have been referred for definitive diagnosis and treatment of pediatric cancer (Table 5). A broad range of incident pediatric malignancies and related disorders were identified in the 8 hospitals, and, despite two decades of incident pediatric cancer cases identified, only 23% were unspecified (Table 4). Of the 137 pediatric cancers identified, 37% were leukemias. Only 10% (13/137) of the pediatric neoplasms were brain tumors and 7% (9/137) were lymphomas, although similar numbers were identified in the earlier (1994-2003) and later (2004-2013) time periods. No retinoblastomas were identified.

Table 5. Pediatric cancers diagnosed 1994-2013* among children residing at birth in the CFCS† catchment area

Types of Pediatric Cancers	Number of cases diagnosed 1994-2003	Number of cases diagnosed 2004-2013	Total (%)
Leukemia	16	34	50 (36.5%)
Acute lymphoblastic leukemia	13	18	31
Acute myeloid leukemia	3	13	16
Myelodysplastic syndrome	0	2	2
Other types of leukemia	0	1	1

Lymphoma	5	4	9 (6.6%)
Hodgkin lymphoma	1	1	2
Non-Hodgkin lymphoma	3	3	6
Other lymphoma	1	0	1
Brain tumors	7	6	13 (9.5%)
Astrocytoma	3	3	6
Medulloblastoma	0	0	0
Primitive neuroectodermal tumor	0	0	0
Other brain tumors	4	3	7
Retinoblastoma	0	0	0
Renal Tumors	8	1	9 (6.6%)
Wilms' tumors	7	1	8
Other renal tumors	1	0	1
Hepatic tumors	3	1	4 (2.9%)
Hepatoblastoma	3	0	3
Other hepatic tumors	0	1	1
Malignant bone tumors	1	2	3 (2.2%)
Osteosarcomas	1	1	2
Other malignant bone tumors	0	1	1
Soft tissue sarcomas	2	1	3 (2.2%)
Rhabdomyosarcoma	2	0	2
Other soft tissue sarcomas	0	1	1
Germ cell tumors	2	10	12 (8.8%)
Testicular cancer	1	0	1
Ovarian tumors	0	4	4
Other germ cell tumors	1	6	7
Carcinomas	1	2	3 (2.2%)
Thyroid cancer	1	2	3
Melanoma	0	0	0
Other types of carcinoma	0	0	0
Unspecified cancers	15	16	31 (22.6%)
TOTAL CANCERS	**60**	**77**	**137**
Other related conditions			
Aplastic anemia	12	26	38
Fanconi anemia	0	1	1

*Diagnosed in 8 hospitals
†CFCS abbreviation = Chinese Children and Families Cohort Study

DISCUSSION

In the pilot study of 580 CIP families, we located all but 3.4% of the families and only 8.7% refused to participate. Overall, 82% of mothers, 79% of fathers and 83% of offspring selected of the 560 families selected completed interviews. More than 90% of those who agreed to be contacted completed interviews, and 99% of the mothers and offspring completed anthropometric measurements. We found notable differences in sociodemographic and lifestyle characteristics between rural and urban parents, but fewer differences in offspring. We identified a broad range of incident (1994-2013) pediatric cancers in the diverse hospitals, but there appeared to be incomplete ascertainment of pediatric brain tumors, lymphomas, and certain others (retinoblastoma), and 23% of unspecified subtype.

Supporting our findings of notable rural vs urban differences in parents, data since the 1990's from the National Bureau of Statistics of China (NBSC) have consistently shown significant differences between rural and urban areas in gross domestic product (GDP), per capita income, and educational attainment.[20] The two pilot study centers differed significantly in geography and urbanicity (rural northeast vs urban southeast regions), gross domestic product (higher in southeast), principal industry (agricultural in the northeast vs high technology industry in the southeast), and greater in-migration in the southeast. Recently household income, education, and health status have been shown to account for the lower use of preventive care services by rural compared to urban residents.[21] We also note significant differences in reported parity and gravidity, consistent with data reported at CIP enrollment in 1993-1995.

The lack of urban-rural differences reported by offspring may reflect adolescent lifestyle changes over time, as illustrated by a recent report on obesity among children in Shandong Province, China.[22] The higher urban compared to rural prevalence of childhood overweight and obesity in Shandong during 1985-2005 no longer existed in 2014 due to the increasing prevalence of overweight and obesity among rural children over time, a change attributed to economic development and lifestyle changes in rural areas.

Strengths and Limitations

Compared with many cohort studies, the proportion of families refusing to participate was relatively small, but strategies should be developed to further minimize refusals and entice higher participation. New strategies are needed to locate offspring who are increasingly likely to move away from their childhood residences for educational or employment opportunities. Although the pilot study included different types of hospitals where children with pediatric cancer might be initially seen and treated, the likely incomplete ascertainment of certain cancer outcomes, a known problem described in compendia of international population-based cancer registry data,[23] suggests the need for learning more about referral patterns for pediatric cancers. Focus groups of hospital and professional society leaders would be useful to discuss strategies for improving identification of pediatric cancer cases, particularly those diagnosed in earlier time periods. In the absence of comprehensive coverage of the geographic catchment area by population-based cancer registries, it is difficult to assess the likely success of matching cohort members with the pediatric cancer cases identified through the hospital component of the pilot study. A more expensive strategy would be to add active follow-up all offspring and parents to identify and verify incident pediatric cancers and to review death certificates of those confirmed as deceased. In the absence of death certificates, particularly in the early time periods, verbal autopsy interviews may be needed.

Overall, the pilot study revealed positive results for re-identifying, tracing, interviewing, and obtaining anthropometric measurements in the original CIP families to establish the new CFCS cohort. A larger feasibility study over a broader geographic region is needed to verify that the strategies used in the current pilot study would continue to yield success in tracing, locating, and obtaining the high participation levels needed for cohort follow-up. The large number of pediatric cancers identified is also promising, but further work is needed to improve the level of ascertainment, and test the feasibility of matching pediatric cancers to the CIP children. If a larger feasibility study is successful, we propose to carry out a prospective record linkage Children and Families Cohort Study (CFCS) to compare risk of pediatric leukemia, brain tumors and other pediatric cancers in offspring of 130,142 Chinese mothers who took vs offspring of 117,689 mothers who did not take periconceptional FA supplements during 1993-1995 to supplement case-control study findings of reduced risks of childhood leukemia associated with mothers' periconceptional use of FA. In addition, the new CFCS cohort would be a valuable scientific resource that could evaluate a wide range of exposures and address many important research questions once assembled.

Dissemination of results and data sharing

The study protocol, data collection instruments, field and coding manuals are available from the corresponding author upon request. If the full-scale study is funded, the findings would be shared with the subjects, public health officials, and medical professionals through newsletters and other types of communication. The main results of the study will also be reported in peer-reviewed scientific journals, and at professional society meetings and international conferences. Qualified researchers can also contact the Steering Committee for the study and seek collaboration with study investigators to carry out additional analyses and other research projects that would use study data.

Contributors

MSL, LW, RJB, AC, LH, LF, ZL, NP, CMK, XL, JS, YW: study concept and design, oversight of all aspects of study, reviewed data, wrote manuscript; NW, PY, XS: Overall supervision of field work and training, and developed operational field manuals; FM: supervised field work and training of interviewers in rural country; RY: supervised field work and training of interviewers in urban county; NW, LF, PY, BW: conducted quality control supervisory visits and other quality control efforts; JF, RJB, AC, LF, MSL, NP: oversaw data entry, manual and electronic data review, and conducted data analysis; LH, LF, SC, MSL, RJB: Responsible for financial supervision; F. Liu, XL, F. Lv, CM, YT, WW, HW, LZ: provided key assistance with access and collaboration of 8 hospitals, developed and reviewed field manual for identifying eligible pediatric cancer cases, oversaw efforts to identify eligible pediatric cancer cases, oversaw abstracting of medical records, reviewed medical record abstracts, and determined final diagnoses of pediatric cancer cases

Conflicts of interest

None declared by any author

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Competing interests

No conflicts of interest or financial disclosures were reported by the authors of this paper.

Ethics approval

The protocol was approved by the institutional ethics review committees including: the National Cancer Institute Special Studies Institutional Review Board (NCI SSIRB - 11CN165 for original and annual renewals); the U.S. Centers for Disease Control and Prevention, which relied on the NCI SSIRB original and annual IRB approvals (CDC protocol 6140); and the Chinese Center for Disease Control and Prevention (CCDC protocol 201110 approved August 8, 2011). Informed written consent was obtained for all aspects of data collection (interviews and anthropometric measurements) from all subjects aged 18 and older. Written assent was obtained from children under age 18. The participants all received certificates of appreciation; mothers received vouchers for purchasing groceries (US$ value = $15); children received memory sticks (US$ value = $7.60. Identification of pediatric cancers diagnosed during 1994-2012 in the catchment area of the original CIP study was carried out within each hospital and data collected were stripped of all personal identifying information before provided to the Chinese CDC and other collaborators.

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Prospective Investigation of Folic Acid Supplements Before and During Early Pregnancy and Pediatric and Adult Cancers in the Chinese Children and Families Cohort: A Pilot Study in a Sample of Rural and Urban Families

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Abbreviations: CDC: Centers for Disease Control and Prevention; CIP = Community Intervention Program; FA = folic acid; MCH = Maternal and Child Health; NCI = National Cancer Institute; NTD = neural tube defects

ABSTRACT

Objective: To determine the feasibility of long-term prospective follow-up and ascertainment of cancer in offspring and mothers from the 1993-1995 Chinese Community Intervention Program that provided folic acid supplements before and during early pregnancy to reduce neural tube defects

Design: Feasibility pilot study for a prospective cohort study

Setting: Families residing during 2012-2013 in one rural and one urban county from 21 counties in 3 provinces in China included in the Community Intervention Program campaign

Participants: The feasibility study targeted 560 families, including 280 from the rural and 280 from the urban county included in the large original study; about half of mothers in each group had taken and half had not taken folic acid supplements.

Intervention: The planned new study is observational.

Primary and secondary outcome measures: Primary: incidence of pediatric cancers in offspring; Secondary: other chronic diseases in offspring and chronic diseases in mothers

Results: Only 3.4% of pilot study families could not be found, 3.9% had moved out of the study area, and 8.8% refused to participate. Interviews were completed by 82% of mothers, 79% of fathers, and 83% of offspring in the 560 families. Almost all mothers and offspring who were interviewed also participated in anthropometric measurements. We found notable urban-rural differences in sociodemographic and lifestyle characteristics of the parents, but fewer differences among the offspring. In eight catchment area hospitals, we identified a broad range of pediatric cancers diagnosed during 1994-2013, although pediatric brain tumors, lymphomas, and rarer cancers were likely under-represented.

Conclusions: Overall, 20 years after the original Community Intervention Program, the pilot study achieved high levels of follow-up and family member interview participation, and identified substantial numbers of pediatric malignancies during 1994-2013 in catchment area hospitals. Next steps and strategies for overcoming limitations are described.

ARTICLE SUMMARY

Strengths and limitations of this study

Strengths

- In the pilot study high proportions of Chinese Community Intervention Program (CIP) mothers, fathers, and offspring were traced, identified, and participated in interviews and anthropometric measurements

Limitations

- Incomplete ascertainment of incident pediatric cancers in the CIP offspring is likely in the absence of long-standing population-based cancer registries of high quality in the geographic region where the intervention was carried out
- Reduction of the small proportion of the CIP pilot study subjects who could not be traced or identified, or would not participate in interviews or anthropometric measurements will be challenging, particularly for those pilot study offspring (and parents) who have moved out of the CIP catchment area

INTRODUCTION

Environmental factors and gene-environment interactions during the periconceptional, prenatal, and early-life periods are increasingly linked with cancer and other serious diseases during childhood, adolescence and adulthood, but research is limited and mechanisms are poorly understood.[1, 2] Support for the *in-utero* origin of pediatric leukemia, mostly acute lymphoblastic leukemia, has been provided by observations on twins showing that the chromosomal rearrangements seen in leukemia cases could occur *in-utero*, coupled with work demonstrating that certain chromosomal translocations are present in the blood spot cards of children who later developed childhood acute lymphoblastic leukemia with the same translocations.[3] The only established risk factors for pediatric cancer (*e.g.* ionizing radiation, a few genetic or congenital syndromes, and birth weight)[4] explain less than 20% of occurrence.[5, 6] Modest increased [7-10] or reduced risks [11, 12] have recently been linked with other exposures in pooled pediatric leukemia case-control studies. Prospects for prevention are limited to avoidance of ionizing radiation or high birth weight, although more recently periconceptional folic acid (FA) supplements have been linked with reduced risks in a large pooled analysis.[11] However, results for the association of periconceptional or prenatal folic acid supplements and pediatric leukemia have been inconsistent in individual studies, and these inconsistencies and the modest associations observed in the pooled analysis may be due in part to differential or inaccurate long-term recall,[13, 14] selection bias[15] and/or declining participation rates, and growing socioeconomic differences between control and case subjects.[16-18] Prospective large epidemiologic studies could overcome many of these limitations.

A unique opportunity to evaluate the potential role of folic acid supplements before and during early pregnancy in reducing risk of pediatric leukemia in offspring was identified 20 years after a 1993-95 Community Intervention Program (CIP) in which FA supplements before and during early pregnancy were provided in 21 Chinese counties to reduce neural tube defects (NTD). Among offspring of 130,142 women who took 400 mcg FA supplements compared with offspring of the 117,689 women who did not take FA supplements, there was a 79% and 41% reduction in the prevalence of NTD in high (northeast) and lower (southeast) rate regions, respectively.[19] Extensive information had been collected during 1993-1995 on maternal sociodemographic, lifestyle, reproductive, medical conditions and treatments, occupational and other factors during the periconceptional and prenatal periods, and on offspring during the early neonatal period.

We conducted a pilot study to assess the feasibility of: (1) establishing a large cohort (designated the Children and Families Cohort Study (CFCS)) from the CIP families for planned prospective epidemiologic studies evaluating pediatric leukemia and other health outcomes in offspring and mothers; (2) collecting data from two generations of family members by interview and anthropometric measurements; and (3) identifying and validating pediatric cancers diagnosed during 1994-2013 in the CIP catchment area among children who are potentially eligible CIP offspring.

METHODS

Study team organization and approvals

In 2012-2013 investigators from the Chinese Center for Disease Control and Prevention (China CDC), U.S. Centers for Disease Control and Prevention (US CDC), the U.S. National Cancer Institute (NCI), the Maternal and Child Health (MCH) Hospital leaders of each county, and clinicians of the hospitals selected for identification of pediatric cancers conducted data collection. The protocol was approved by the Chinese provincial, city, and county health bureaus, county MCH hospitals and other participating hospitals, and by the Chinese and US CDCs and US NCI ethics review committees (see details in Ethics Approval section following the Discussion).

Study sample

Five hundred CIP families were targeted from two CIP geographic regions, *e.g.*, a rural county in the northeast and an urban county in the southeast. From the pregnancy-monitoring registration system, 280 families from each county were selected with eligibility criteria including: 1) mother resided and underwent a premarital or prenatal physical exam in the specified county during 1993-1995; 2) the pregnancy resulted in a live, single birth in the county by December 1996; 3) sex of the infant was known, and 4) high quality data on maternal use of FA supplements before and during the pregnancy was available.

Tracing and contacting families

County MCH staff verified the names, vital status, current addresses, and phone numbers of eligible mothers and children selected by comparing the lists with township and village health service and New Rural Cooperative Insurance rosters. To improve recruitment, the county-level MCH, township hospital, village or community health service center physicians, assisted by the village development and community/street committee staff, made initial contact with the families.

A letter describing the study purpose, questionnaire topics, and physical measurements, confidentiality, benefits, potential risks, incentives, and opportunity to opt out of all or part of the data collection was mailed or delivered in person. After letter delivery, the village or Township doctor contacted the mother/caretaker to answer questions, and arrange a home visit where consent was obtained.

Interviewer training

After a didactic 2-day training, interviewers practiced questionnaire administration and taking anthropometric measurements. The training concluded with instructions on manual review and data editing. Approximately one month later, supervisory Chinese CDC staff again evaluated staff, and re-trained as needed.

Data collection: questionnaires

One of two questionnaires assessed family residential characteristics and maternal sociodemographic characteristics, lifestyle, reproductive and medical history, and job history. If the child resided with a caretaker, a modified shorter questionnaire was administered. A second maternal/caretaker questionnaire asked about the offspring's date of birth, vital status, history of cancer or birth defects, diagnosis of autism, developmental milestones, highest level of education, and job history.

The offspring’s questionnaire asked date of birth, self-rating of physical health, source of medical care, number of non-routine health visits in the past 12 months, cigarette smoking and second-hand smoke history, use of alcohol, and history of pubertal changes.

The father’s questionnaire inquired about date of birth, education, marital status, job history, smoking and second-hand smoking, alcohol use, and medical history.

Other data collection (results reported separately)

After the interviews, offspring and mothers were invited to participate in anthropometric measurements at the Township hospitals. At the end of questionnaire and anthropometric measurements data collection, the participants received appreciation certificates and incentives. A letter was also provided indicating that the participant might be contacted for a second study to assess diet, nutrition, physical activity, and ultraviolet radiation exposure.

Identification and validation of pediatric cancer cases

In consultation with hospitals and community leaders, 8 hospitals providing different levels of services were selected from study regions and major cities near to the catchment area where CIP children might have been referred for diagnosis and treatment of pediatric cancer. A workshop was held with experts in pediatric hematology, oncology, and neurosurgery from these hospitals to develop the methods for identification and validation of the pediatric cancer outcomes.

The medical record review process included: (1) searching for medical records to identify all pediatric cancer patients born during 1994-1996 who were diagnosed and/or treated during 1994-

2013; (2) developing a list of all potentially eligible patients (born during 1994-1996 in the 21 counties included in the CIP or, if no specific place of birth was listed, those born in the three provinces in which the 21 counties were geographically located); (3) obtaining and abstracting medical records of these patients; and (4) independent reviewing of the abstract forms by two clinical experts with resolution of differences through discussion to determine a final diagnosis. For quality control purposes, each hospital was visited at least once by China CDC staff to evaluate procedures. In the absence of re-identification of the entire CIP cohort and comprehensive population-based cancer registries, it was not possible to link the pediatric cancer cases identified in hospitals with the cohort.

Data management

A data management training workshop was held in Beijing for China CDC staff followed by a detailed review and editing of the data collected. All forms were coded, checked, entered twice, and data verified for accuracy. Range and logic sequences were verified against original paper forms and corrections made as required.

Statistical analysis

In data analysis conducted during 2016-2017, cross-tabulation was used to evaluate the distribution of demographic, socioeconomic, lifestyle, developmental and medical history characteristics by county. Fisher's Exact tests were used to test for urban versus rural geographic differences by covariates among mothers, offspring, and fathers.

Subjects and public involvement

Subjects and the public were not involved in development of the research question, the study design, determination of the outcome measures to be studied, recruitment or conduct of the study. Subjects were informed about results of anthropometric measures and blood chemistry laboratory tests (methods for the laboratory test components of a second pilot study are reported elsewhere). Subjects also received physical activity monitors at the end of the physical activity monitoring component of the second pilot study (methods reported elsewhere).

If the full-scale study is funded, the findings would be shared with the subjects, public health officials, and medical professionals through newsletters and other types of communication.

RESULTS

Of the 560 families selected for the pilot study, only 3% (2% in the rural and 5% in the urban center) could not be found, 4% of families reportedly moved away (6% in the rural and 2% in the urban center), and 9% (8% in the rural and 9% in the urban center) refused to be contacted (Table 1). Overall, 82% of mothers, 79% of fathers and 83% of offspring completed interviews of the 560 families selected. Among the 469 families (84% of the 560 selected) targeted for interviews (after excluding those who could not be found, had moved away, or had refused to be contacted) the interview participation was very high, e.g., 98% of mothers, 95% of fathers, and 99% of offspring. Almost all mothers and offspring who were interviewed also participated in the anthropometric measurements (Table 1). The proportion of mothers contacted who took FA supplements (49% in the rural center, 52% in the urban center) was similar to the 50% in each center who took FA in the samples originally selected.

Table 1. Population targeted for pilot study, description of participants, reasons for non-participation, and residential and sociodemographic characteristics of participating families

Population targeted, description of participants and reasons for non-participation in pilot study	Rural area N (%)	Urban area N (%)	Both areas N (%)	P-value*
Number of families selected for pilot	280	280	560	
Families selected but not included	46 (16.4%)	45 (16.1%)	91 (16.3%)	
Reason not included				
Moved away	17 (6.1%)	5 (1.8%)	22 (3.9%)	
Not found	6 (2.1%)	13 (4.6%)	19 (3.4%)	
Refused	23 (8.2%)	26 (9.3%)	49 (8.8%)	
Mother deceased	0	1 (0.3%)	1 (0.1%)	
Families targeted for interviews†	234 (83.6%)	235 (83.9%)	469 (83.8%)	
Mothers who consented among families targeted for interview	229 (97.9%)	231 (98.3%)	460 (98.1%)	
Mothers: Completed interview‡	229 (81.8%)	231 (82.5%)	460 (92.1%)	
Physical measurements§	228 (99.6%)	230 (99.6%)	458 (99.6%)	
Fathers: Completed interview‡	232 (82.9%)	212 (75.7%)	444 (79.3%)	
Children: Completed interview‡	233 (83.2%)	229 (81.8%)	462 (82.5%)	
Physical measurements§	231 (99%)	229(100%)	460 (99.6%)	
Caretakers: Completed interview¶	6	9	15	
Residential and sociodemographic characteristics of participating families				
Number of years at current home				
<=10	23 (10%)	111 (48%)	134 (29%)	<.0001
11–19	138 (59%)	76 (33%)	214 (46%)	
20+	71 (31%)	45 (19%)	116 (25%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Own or rent home				
Own	224 (97%)	216 (93%)	440 (95%)	0.0572
Rent	7 (3%)	17 (7%)	24 (5%)	
Unknown	1 (0.4%)	0	1 (0.2%)	
Highest number of persons residing in residence in the past year				
<=3	100 (43%)	97 (42%)	197 (42%)	<.0001
4	83 (36%)	26 (11%)	109 (23%)	
>=5	49 (21%)	110 (47%)	159 (34%)	

*Fisher's Exact test for rural vs urban differences

†Targeted for interviews were those who had not moved away, could be found, did not refuse, or mother not deceased

‡Percents shown are the proportion completing interviews of those selected for the pilot study

§Percents are the proportions who completed physical measurements of those who were interviewed

¶If mother not available, caretaker information was used

Nearly half of urban families resided 10 or fewer years in their current home whereas 90% of rural families had lived more than 10 years in the current home (Table 1). More than 93% of rural and urban families owned their current home. Close to half of the urban families compared to 21% of rural families had 5 or more persons recently residing in their residence.

Urban mothers were younger at the age of marriage registration, birth of the CIP offspring, and at the age of current interview completion (Table 2). Rural mothers reported less education, held fewer jobs, and a slightly higher proportion were married compared with urban mothers. Almost none of the rural and urban mothers reported smoking cigarettes. Rural mothers (43%) were somewhat more likely than urban mothers (33%) to report being exposed to secondhand smoke during their pregnancies for 3 or more days per week. Rural mothers (45%) were more likely than urban mothers (35%) to report that their offspring had been exposed to secondhand smoke 3 or more days per week before age 5 years. Few of the mothers (5% overall, 8% urban versus 1% rural) reported drinking alcohol. Rural mothers were more likely to report onset of menstrual periods at older ages, and 30% of rural compared with 16% of urban mothers reported only one pregnancy.

Table 2. Maternal sociodemographic, lifestyle and reproductive characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=229 (%)	Urban area N=231 (%)	Both areas N=460 (%)	P-value *
Age at CIP enrollment / marriage registration				
<=22	84 (37%)	126 (55%)	210 (46%)	0.0004
23-24	66 (29%)	59 (26%)	125 (27%)	
>=25	79 (34%)	46 (20%)	125 (27%)	
Age at first birth				
<=23	88 (38%)	132 (57%)	220 (48%)	<.0001
24-25	58 (25%)	57 (25%)	115 (25%)	

Characteristics	Rural area N=229 (%)	Urban area N=231 (%)	Both areas N=460 (%)	P-value [*]
>=26	83 (36%)	42 (18%)	125 (27%)	
Age at CFCS interview completion				
<=39	70 (31%)	116 (50%)	186 (40%)	<.0001
40-41	72 (31%)	67 (29%)	139 (30%)	
>=42	87 (38%)	48 (21%)	135 (29%)	
Highest level of education				
None	3 (1%)	1 (0.4%)	4 (1%)	<.0001
Some or all elementary school	42 (18%)	17 (7%)	59 (13%)	
Completed middle school	144 (63%)	143 (62%)	287 (62%)	
Completed high school/ technical school	39 (17%)	46 (20%)	85 (18%)	
Completed some or all college/university	1 (0.4%)	24 (10%)	25 (5%)	
Current marital status				
Married	227 (99%)	216 (94%)	443 (96%)	0.0002
Widowed	2 (1%)	1 (0.4%)	3 (1%)	
Divorced	0	12 (5%)	12 (3%)	
Other	0	2 (1%)	2 (0.4%)	
Current number of jobs after completed school				
None	0	1 (0.4%)	1 (0.2%)	<.0001
1	158 (69%)	21 (9%)	179 (39%)	
2	48 (21%)	68 (29%)	116 (25%)	
3+	23 (10%)	141 (61%)	164 (36%)	
Smoking/Secondhand Smoke [*]				
Never smoked cigarettes regularly	227 (99%)	230 (100%)	457 (99%)	0.6225
Exposed to secondhand smoke at home >10 years before age 20	91 (40%)	79 (34%)	170 (37%)	0.2872
Exposed to secondhand smoke at home >10 years after age 20	125 (55%)	122 (53%)	247 (54%)	0.5299
Exposed to secondhand smoke during CIP pregnancy for 3 or more days per week	99 (43%)	77 (33%)	176 (38%)	0.0689
Child exposure to secondhand smoke before age 5 years				
None	101 (44%)	105 (45%)	206 (45%)	0.0088
<3 days per week	22 (10%)	43 (19%)	65 (14%)	
3+ days per week	103 (45%)	80 (35%)	183 (40%)	
Unknown	3 (1%)	3 (1%)	6 (1%)	
Ever drink alcohol				
No/less than once per month	226 (99%)	213 (92%)	439 (95%)	0.0012

Characteristics	Rural area N=229 (%)	Urban area N=231 (%)	Both areas N=460 (%)	P-value [*]
Yes	3 (1%)	18 (8%)	21 (5%)	
Age menstrual periods started				
12-13	29 (13%)	47 (20%)	76 (17%)	0.0497
14-15	120 (52%)	122 (53%)	242 (53%)	
16+	78 (34%)	62 (27%)	140 (30%)	
Unknown	2 (1%)	0	2 (0.4%)	
Number of pregnancies				
1	68 (30%)	37 (16%)	105 (23%)	0.0002
2	95 (41%)	86 (37%)	181 (39%)	
3	53 (23%)	74 (32%)	127 (28%)	
4+	13 (6%)	34 (15%)	47 (10%)	

[*] Fisher's Exact test for rural vs urban differences

Rural fathers were older at the time of marriage registration, birth of their offspring, and at the current interview compared with urban fathers (Table 3). Rural fathers reported less education and fewer jobs compared with urban fathers. A higher proportion of rural (33%) compared with urban (19%) fathers reported never smoking, although rural fathers were more likely than urban fathers to be exposed to secondhand smoke for over ten years before age 20. Urban (75%) compared to rural (60%) fathers were more likely to be currently smoking. Use of alcohol was similar between rural (63%) and urban (65%) fathers, but a somewhat higher proportion of urban (61%) than rural (57%) fathers reported alcohol use for 15 or more years.

Table 3. Paternal sociodemographic and lifestyle characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=232 (%)	Urban area N=212 (%)	Both areas N=444 (%)	P-value [*]
Age at CIP enrollment / marriage registration				
<=22	77 (33%)	85 (40%)	162 (36%)	0.0030
23-24	56 (24%)	69 (33%)	125 (28%)	
>=25	99 (43%)	58 (27%)	157 (35%)	
Age at birth of child				
<=23	71 (31%)	91 (43%)	162 (36%)	0.0002

Characteristics	Rural area N=232 (%)	Urban area N=212 (%)	Both areas N=444 (%)	P-value *
24-25	59 (25%)	67 (32%)	126 (28%)	
>=26	102 (44%)	54 (25%)	156 (35%)	
Age at CFCS interview completion				
<=39	58 (25%)	77 (36%)	135 (30%)	0.0038
40-41	68 (29%)	69 (33%)	137 (31%)	
>=42	106 (46%)	66 (31%)	172 (39%)	
Highest level of Education				
None	1 (0.4%)	0	1 (0.2%)	<.0001
Some or all elementary school	43 (19%)	16 (8%)	59 (13%)	
Completed middle school	153 (66%)	125 (59%)	278 (63%)	
Completed high school/technical school	32 (14%)	49 (23%)	81 (18%)	
Completed some or all college/university	3 (1%)	22 (10%)	25 (6%)	
Number of jobs after completed school				
1	146 (63%)	28 (13%)	174 (39%)	<.0001
2	63 (27%)	65 (31%)	128 (29%)	
3+	23 (10%)	119 (56%)	142 (32%)	
Currently smoking cigarettes				
Never Smoked	77 (33%)	40 (19%)	117 (26%)	0.0008
No	16 (7%)	13 (6%)	29 (7%)	
Yes	139 (60%)	159 (75%)	298 (67%)	
Secondhand Smoke*				
Exposed to secondhand smoke at home >10 years before age 20	103 (44%)	73 (34%)	176 (40%)	0.0275
Exposed to secondhand smoke at home >10 years after age 20	53 (23%)	56 (26%)	109 (25%)	0.7922
Use of alcohol				
No/less than once per month	86 (37%)	74 (35%)	160 (36%)	0.6924
Yes	146 (63%)	138 (65%)	284 (64%)	
Use of alcohol in years				
Never	86 (37%)	74 (35%)	160 (36%)	<.0001
<15	1 (0.4%)	2 (1%)	3 (1%)	
15-19	8 (3%)	36 (17%)	44 (10%)	
20+	125 (54%)	94 (44%)	219 (49%)	
Unknown	12 (5%)	6 (3%)	18 (4%)	

*Fisher's Exact test for rural vs urban differences

Urban versus rural differences in sociodemographic factors were less apparent among offspring (Table 4). The two groups were similar in birth year, age at interview, and sex distribution, but somewhat more urban than rural offspring reported living with their parents. Most in each group were full-time students, but urban offspring were more likely to report attending trade or technical school. Most offspring in both groups reported never smoking cigarettes regularly; a somewhat higher proportion of urban than rural offspring reported secondhand smoke exposure at home for 1 or more days per week and alcohol use for one or more days since birth.

Table 4. Offspring sociodemographic and lifestyle characteristics, Chinese Children and Families Cohort Study questionnaire, 2013

Characteristics	Rural area N=233 (%)	Urban area N=229 (%)	Both areas N=462 (%)	P-value*
Year of birth				
1994	67 (29%)	70 (31%)	137 (30%)	0.7667
1995	106 (45%)	96 (42%)	202 (44%)	
1996	60 (26%)	62 (27%)	122 (26%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Age at interview completion				
<16	88 (38%)	82 (36%)	170 (37%)	0.5264
16	93 (40%)	102 (45%)	195 (42%)	
17+	52 (22%)	44 (19%)	96 (21%)	
Unknown	0	1 (0.4%)	1 (0.2%)	
Sex				
Female	120 (52%)	112 (49%)	232 (50%)	0.6418
Male	113 (48%)	117 (51%)	230 (50%)	
Living arrangements				
Living with parents	211 (91%)	221 (97%)	432 (94%)	0.0001
Living with grandparents or other adult guardian	1 (0.4%)	3 (1%)	4 (1%)	

Characteristics	Rural area N=233 (%)	Urban area N=229 (%)	Both areas N=462 (%)	P-value*
Other	15 (6%)	0	15 (3%)	
Unknown	6 (2.6%)	5 (2.2%)	11 (2.4%)	
Current activity: school, work, other				
Full-time student	215 (92%)	208 (91%)	423 (92%)	0.2205
Working part-time and attending school part-time	0	3 (1%)	3 (1%)	
Working	6 (3%)	3 (1%)	9 (2%)	
Not working and not attending school	7 (3%)	10 (4%)	17 (3.7%)	
Unknown	5 (2%)	5 (2.4%)	10 (2.2%)	
Highest level of Education				
Junior high school	43 (18%)	18 (8%)	61 (13%)	<.0001
Senior high school	123 (53%)	94 (41%)	217 (47%)	
Trade or technical school	49 (21%)	99 (43%)	148 (32%)	
Unknown	18 (8%)	18 (8%)	36 (8%)	
Ever smoked cigarettes regularly				
No	223 (96%)	215 (94%)	438 (95%)	0.4085
Yes	10 (4%)	14 (6%)	24 (5%)	
Number of days exposed to second hand smoke where you live in past week				
0	158 (68%)	143 (62%)	301 (65%)	0.0269
1-4	33 (14%)	55 (24%)	88 (19%)	
5+	38 (16%)	30 (13%)	68 (15%)	
Unknown	4 (2%)	1 (0.4%)	5 (1%)	
Number of days ever drank alcohol since birth				
Never	199 (85%)	133 (58%)	332 (72%)	<.0001
1-2	14 (6%)	40 (17%)	54 (12%)	
3-9	11 (5%)	29 (13%)	40 (9%)	
10-19	2 (1%)	10 (4%)	12 (3%)	
≥ 20	5 (2%)	13 (6%)	18 (4%)	
Unknown	2 (1%)	4 (2%)	6 (1%)	

*Fisher's Exact test for rural vs urban differences

Eight hospitals selected included county and provincial hospitals, children's medical centers, and referral hospitals in the nearby cities of Beijing (treating brain tumors), Tianjin (hematologic disorders), and Shanghai (pediatric oncology) to which children would have been referred for definitive diagnosis and treatment of pediatric cancer (Table 5). A broad range of incident pediatric malignancies and related disorders were identified in the 8 hospitals; of the total cancers, 77% were designated by type and 23% were unspecified (Table 4). Of the 137 pediatric cancers identified, 37% were leukemias. Only 10% (13/137) of the pediatric neoplasms were brain tumors and 7% (9/137) were lymphomas, although similar numbers were identified in the earlier (1994-2003) and later (2004-2013) time periods. No retinoblastomas were identified.

Table 5. Pediatric cancers diagnosed 1994-2013* among children residing at birth in the CFCS† catchment area

Types of Pediatric Cancers	Number of cases diagnosed 1994-2003	Number of cases diagnosed 2004-2013	Total (%)
Leukemia	16	34	50 (36.5%)
Acute lymphoblastic leukemia	13	18	31
Acute myeloid leukemia	3	13	16
Myelodysplastic syndrome	0	2	2
Other types of leukemia	0	1	1
Lymphoma	5	4	9 (6.6%)
Hodgkin lymphoma	1	1	2
Non-Hodgkin lymphoma	3	3	6
Other lymphoma	1	0	1
Brain tumors	7	6	13 (9.5%)
Astrocytoma	3	3	6
Medulloblastoma	0	0	0
Primitive neuroectodermal tumor	0	0	0
Other brain tumors	4	3	7
Retinoblastoma	0	0	0
Renal Tumors	8	1	9 (6.6%)
Wilms' tumors	7	1	8
Other renal tumors	1	0	1
Hepatic tumors	3	1	4 (2.9%)
Hepatoblastoma	3	0	3
Other hepatic tumors	0	1	1

Malignant bone tumors	1	2	3 (2.2%)
Osteosarcomas	1	1	2
Other malignant bone tumors	0	1	1
Soft tissue sarcomas	2	1	3 (2.2%)
Rhabdomyosarcoma	2	0	2
Other soft tissue sarcomas	0	1	1
Germ cell tumors	2	10	12 (8.8%)
Testicular cancer	1	0	1
Ovarian tumors	0	4	4
Other germ cell tumors	1	6	7
Carcinomas	1	2	3 (2.2%)
Thyroid cancer	1	2	3
Melanoma	0	0	0
Other types of carcinoma	0	0	0
Unspecified cancers	15	16	31 (22.6%)
TOTAL CANCERS	**60**	**77**	**137**
Other related conditions			
Aplastic anemia	12	26	38
Fanconi anemia	0	1	1

*Diagnosed in 8 hospitals
†CFCS abbreviation = Chinese Children and Families Cohort Study

DISCUSSION

In the pilot study of 580 CIP families, we located all but 3.4% of the families and only 8.7% refused to participate. Overall, 82% of mothers, 79% of fathers and 83% of offspring selected of the 560 families selected completed interviews. More than 90% of those who agreed to be contacted completed interviews, and 99% of the mothers and offspring completed anthropometric measurements. We found notable differences in sociodemographic and lifestyle characteristics between rural and urban parents, but fewer differences in offspring. We identified a broad range of incident (1994-2013) pediatric cancers in the diverse hospitals, but there appeared to be incomplete ascertainment of pediatric brain tumors, lymphomas, and certain others (retinoblastoma), and 23% were of unspecified subtype.

Supporting our findings of notable rural vs urban differences in parents, data since the 1990's from the National Bureau of Statistics of China (NBSC) have consistently shown significant differences between rural and urban areas in gross domestic product (GDP), per capita income, and educational attainment.[20] The two pilot study centers differed significantly in geography and urbanicity (rural northeast vs urban southeast regions), gross domestic product (higher in southeast), principal industry (agricultural in the northeast vs high technology industry in the southeast), and greater in-migration in the southeast. Recently, household income, education, and health status have been shown to account for the lower use of preventive care services by rural compared to urban residents.[21] We also note significant differences in reported parity and gravidity, consistent with data reported at CIP enrollment in 1993-1995.

The lack of urban-rural differences reported by offspring may reflect adolescent lifestyle changes over time, as illustrated by a recent report on obesity among children in Shandong Province, China.[22] The higher urban compared to rural prevalence of childhood overweight and obesity in Shandong during 1985-2005 no longer existed in 2014 due to the increasing prevalence of overweight and obesity among rural children over time, a change attributed to economic development and lifestyle changes in rural areas.

Strengths and Limitations

Compared with many cohort studies, the proportion of families refusing to participate was relatively small, but strategies should be developed to further minimize refusals and entice higher participation. New strategies are needed to locate offspring who are increasingly likely to move away from their childhood residences for educational or employment opportunities. The ideal approach for identifying incident pediatric cancers in the Chinese Children and Families Cohort Study would have been linkage with population-based cancer registries, but there have been no long-standing population-based cancer registries of high quality in the geographic regions where the original CIP was carried out. Although the pilot study included different types of hospitals where children with pediatric cancer might be initially seen and treated, the likely incomplete ascertainment of certain cancer outcomes, a known problem described in compendia of international population-based cancer registry data,[23] suggests the need for learning more about referral patterns for pediatric cancers. Focus groups of hospital and medical professional society leaders would be useful to discuss strategies for improving identification of pediatric cancer cases, particularly those diagnosed in earlier time periods. In the absence of comprehensive coverage of the geographic catchment area by high-quality population-based cancer registries, it is difficult to assess the likely success of matching cohort members with the pediatric cancer cases identified through the hospital component of the pilot study. A more expensive strategy would be to add active follow-up all offspring and parents to identify and verify incident pediatric cancers and to review death certificates to confirm those reported as deceased. In the absence of death certificates, particularly in the early time periods, verbal autopsy interviews may be needed.

Overall, the pilot study revealed positive results for re-identifying, tracing, interviewing, and obtaining anthropometric measurements in the original CIP families to establish the new CFCS cohort. A larger feasibility study over a broader geographic region is needed to verify that the strategies used in the current pilot study would continue to yield success in tracing, locating, and obtaining the high participation levels needed for cohort follow-up. The large number of pediatric cancers identified is also promising, but further work is needed to improve the level of ascertainment, and test the feasibility of matching pediatric cancers to the CIP children. If a larger feasibility study is successful, we propose to carry out a prospective record linkage Children and Families Cohort Study (CFCS) to compare risk of pediatric leukemia, brain tumors and other pediatric cancers in offspring of 130,142 Chinese mothers who took vs offspring of 117,689 mothers who did not take FA supplements before and during early pregnancy in the 1993-1995 CIP to supplement case-control study findings of reduced risks of childhood leukemia associated with mothers' periconceptional use of FA. In addition, the new CFCS cohort would be a valuable scientific resource that could evaluate a wide range of exposures and outcomes, and address many important research questions once assembled.

Dissemination of results and data sharing

The study protocol, data collection instruments, field and coding manuals are available from the corresponding author upon request. If the full-scale study is funded, the findings would be shared with the subjects, public health officials, and medical professionals through newsletters and other types of communication. The main results of the study will also be reported in peer-reviewed scientific journals, and at professional society meetings and international conferences. Qualified researchers can also contact the Steering Committee for the study and seek collaboration with study investigators in research projects that would use study data.

Contributors

MSL, LW, RJB, AC, LH, LF, ZL, NP, CMK, XL, JS, YW: study concept and design, oversight of all aspects of study, reviewed data, wrote manuscript; NW, PY, XS: Overall supervision of field work and training, and development of operational field manuals; FM: supervised field work and training of interviewers in rural country; RY: supervised field work and training of interviewers in urban county; NW, LF, PY, BW: conducted quality control supervisory visits and other quality control efforts; JF, RJB, AC, LF, MSL, NP: oversaw data entry, manual and electronic data review, and conducted data analysis; LH, LF, SC, MSL, RJB: responsible for financial supervision; FL, XL, F. Lv, CM, YT, WW, HW, LZ: provided key assistance with access and collaboration of 8 hospitals, developed and reviewed the field manual for identifying eligible pediatric cancer cases, oversaw efforts to identify eligible pediatric cancer cases, oversaw abstracting of medical records, reviewed medical record abstracts, and determined final diagnoses of pediatric cancer cases

Conflicts of interest

None declared by any author

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Competing interests

No conflicts of interest or financial disclosures were reported by the authors of this paper.

Ethics approval

The protocol was approved by the institutional ethics review committees including: the National Cancer Institute Special Studies Institutional Review Board (NCI SSIRB - 11CN165 for original and annual renewals); the U.S. Centers for Disease Control and Prevention, which relied on the NCI SSIRB original and annual IRB approvals (CDC protocol 6140); and the Chinese Center for Disease Control and Prevention (CCDC protocol 201110 approved August 8, 2011). Informed written consent was obtained for all aspects of data collection (interviews and anthropometric measurements) from all subjects aged 18 and older. Written assent was obtained from children under age 18. The participants all received certificates of appreciation; mothers received vouchers for purchasing groceries (US$ value = $15); children received memory sticks (US$ value = $7.60. Identification of pediatric cancers diagnosed during 1994-2012 in the catchment area of the original CIP study was carried out within each hospital and data collected were stripped of all personal identifying information before being provided to the Chinese CDC and other collaborators.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	See title "Prospective investigation of folic acid supplements before and during early pregnancy and pediatric and adult cancers in the Chinese Children and Families Cohort: A pilot study in a sample of urban and rural families"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5	See abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8	See paras 1- 3 of Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	6-7	See Introduction, para 3: "We conducted a pilot study to assess the feasibility of: (1) establishing a large cohort (designated the Children and Families Cohort Study (CFCS)) from the CIP [Community Intervention Program] families for planned prospective epidemiologic studies evaluating pediatric leukemia and other health outcomes in offspring and mothers; (2) collecting data from two generations of family members by interview and anthropometric measurements; and (3) identifying and validating pediatric cancers diagnosed during 1994-2013 in the CIP catchment area among children who are potentially eligible CIP offspring."

Methods				
Study design	4	Present key elements of study design early in the paper	9 and 11	See Methods sections entitled "Study sample" and "Identification and validation of pediatric cancer cases"
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8, 9, and 11	See Methods sections entitled: "Study team organization and approvals" for dates of data collection; "Study sample" for setting, location, relevant dates for choosing the sample of subjects to be identified and traced; and "Identification and validation of pediatric cancer cases" for setting, locations, and period of diagnosis of cases
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9 and 11	(a) Pilot investigation for future cohort study: see "Study sample" for eligibility criteria and sources and methods of selection of pilot study subjects; see "Identification and validation of pediatric cancer cases" for description of methods to identify potentially eligible pediatric cancer cases and years of diagnosis in this pilot study
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per		NA

		case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-12	See Methods section "Identification and validation of pediatric cancer cases" for definition of pediatric cancer outcomes to be assessed and the approach used for validation; see "Data collection: questionnaires" section for a list of the major categories of characteristics to be ascertained in the pilot study interview; see "Other data collection" for the other data to be collected (anthropometric measurements); see lists of variables shown in Tables 1-4 that would be evaluated as potential confounders and effect modifiers in the future full-scale cohort investigation
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12	See Methods sections for sources of data that included: pregnancy monitoring registration system for identifying the study sample (see "Study sample"); multiple sources for tracing families (see "Tracing and contacting families"); questionnaires for subject characteristics and exposures (see "Data collection:

				questionnaires"); anthropometric measurements (see "Other data collection"); and medical record (see "Identification and validation of pediatric cancer cases").
Bias	9	Describe any efforts to address potential sources of bias		NA for the objectives of this pilot study
Study size	10	Explain how the study size was arrived at	13, 19	The goal of the pilot study was to test feasibility among families selected such that: half resided in urban and half in rural areas, half of mothers took folic acid supplements and half did not, half of offspring were male and half were female, the size of the pilot study would be sufficiently large to estimate feasibility and the costs to conduct the pilot study could be supported with the available budget (see Results, paragraph 1, and Tables 1 (number of families selected for pilot) and 4 (sex of offspring)

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	14-21	Tables show frequency distributions; many variables had straightforward categories (*e.g.*, year of birth [births occurred during 3 years, e.g., 1994-1996], age at interview [only 3 birth years], sex [2], number of pregnancies [4], subtypes of pediatric cancers [widely used classification]; other categories were based on standard categories used in many studies (*e.g.*, age menstrual periods started) or previous studies in China (*e.g.*, highest level of education completed)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12	See "Statistical Methods" section; confounding was not controlled for in this pilot study
		(*b*) Describe any methods used to examine subgroups and interactions	13-21	See Tables 1-5 showing frequency distributions; interactions were not evaluated in this pilot study
		(*c*) Explain how missing data were addressed	13-20	Unknown/missing data on variables is shown in tables for descriptive purposes, but not included in analyses
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		NA for this pilot study
		(*e*) Describe any sensitivity analyses		NA for this pilot study
Results				

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14	See Table 1 and Results para 1
		(b) Give reasons for non-participation at each stage	13	See Results, para 1
		(c) Consider use of a flow diagram		Considered, but decided not to include because of small size and straightforward nature of the pilot study
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13-20	See Tables 1-4
		(b) Indicate number of participants with missing data for each variable of interest	Table 1	The numbers of subjects with missing data on certain variables is detailed in Table 1; data missing for categories of variables assessed in interviews of mothers, fathers, and offspring is shown in Tables 2, 3, and 4, respectively.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		NA for this pilot study
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	21	See Table 5 of potential number of pediatric cancers
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		NA
		Cross-sectional study—Report numbers of outcome events or summary measures		NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		NA for this pilot study
		(*b*) Report category boundaries when continuous variables were categorized		NA for this pilot study
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA for this pilot study

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		NA for this pilot study
Discussion				
Key results	18	Summarise key results with reference to study objectives	22	See Discussion, para 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24	See Discussion, para 4
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24	See Discussion, para 5 (concluding paragraph)
Generalisability	21	Discuss the generalisability (external validity) of the study results		NA for this pilot study
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26	The study was funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute and the U.S. Public Health Service of the Department of Health and Human Services; cooperative agreements from the U.S. Centers for Disease Control and Prevention, and internal funding from the Chinese Center for Disease Control and Prevention (see section entitled Funding, page 26).

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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